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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,263	07/11/2007	James Russell	RUSSELL6	9299

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EXAMINER	
SHAW, AMANDA MARIE	

ART UNIT	PAPER NUMBER
1634	

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03/30/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,263	RUSSELL ET AL.	
	Examiner	Art Unit	
	AMANDA SHAW	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2012*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *36,44-47,60,61,68,88,92 and 93* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *36,44-47,60,61,68,88,92 and 93* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/27/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed March 19, 2012. Applicant's remarks and amendments have been fully and carefully considered but are not found to be sufficient to put the application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicant's amendments. Any rejections or objections not reiterated herein have been withdrawn. This action is made FINAL.

2. Claims 36, 44-47, 60-61, 68, 88, and 92-93 are currently pending.

Additionally it is noted that Applicants have elected the following species for examination:

A. the Protein C sequence (SEQ ID NO: 1)

B. the SNP at position 4732 of the Protein C sequence (SEQ ID NO: 1)

C. systemic inflammatory response syndrome (SIRS) as the disease

D. activated protein C as the anti-inflammatory agent

Withdrawn Rejections

2. The rejection made under 35 USC 101 in section 4 of the Office Action of September 20, 2011 is moot in view of the cancellation of all of the previously rejected claims.

The rejection made under 35 USC 112 1st paragraph (written description) in section 6 of the Office Action of September 20, 2011 is moot in view of the cancellation of all of the previously rejected claims.

The rejection made under 35 USC 103 in section 10 of the Office Action of September 20, 2011 is moot in view of the cancellation of all of the previously rejected claims.

Claim Rejections - 35 USC § 112 1st paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36, 44-47, 60-61, 68, 88, and 92-93 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for:

A method of treating SIRS in a human subject, the method comprising: obtaining a nucleic acid sample from said subject; assaying said nucleic acid sample to determine the identity of the alleles present at position 4732 of SEQ ID NO: 1; determining that said patient that is homozygous for the C allele or heterozygous for the C/T alleles at position 4732 of SEQ ID NO: 1 is at risk for decreased survival and increased multiple organ dysfunction; and administering to said subject activated protein C.

does not reasonably provide enablement for claims which encompass (a) any genotype in linkage disequilibrium with position 4732 of SEQ ID NO: 1; and (b) any combination of genotypes in linkage disequilibrium with position 4732 of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the Invention

The claims are drawn to a methods for treating SIRS in a human subject in need thereof. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

The breadth of the claims

Claims 36, 44-47, 60, 61, , 68, 88, and 92-93 are drawn to a method of treating SIRS in a human subject in need thereof. The method comprises (a) selecting a human subject having a risk genotype for SIRS, when the subject has one or more of the following genotypes at one or more of the following positions: (i) CC or CT at 4732 of SEQ ID NO:1; (ii) a genotype in linkage disequilibrium with position 4732 of SEQ ID NO: 1; or (iii) a combination of genotypes which are in linkage disequilibrium with position 4732 in SEQ ID NO:1; and (b) administering to said human subject selected in (a) an activated protein C.

The claims encompass the following genotypes in LD with position 4732 of SEQ ID NO: 1: AA or AG at 4813, GG or GA at 6379, AA or AG at 6762, CC or C- at 7779, TT or TC at 8058, TT or TG at 8915 or TT or TC at 12228 of SEQ ID NO: 1.

The claims encompass the following combinations of genotypes in LD with position 4732 of SEQ ID NO: 1: (1) CC or CA at 9198 and AA or AG at 5867; (2) CC or

CA at 9198 and GG or GC at 4800; (3) AA or AG at 3220 and AA or AG at 5867; and (4) AA or AG at 3220 and GG or GC of 4800.

Guidance in the Specification and Working Examples

Example 2 in the specification teaches an association between the C allele at position 4732 of SEQ ID NO: 1 and altered survival and organ dysfunction in critically ill adults with SIRS. Specifically the specification teaches that in human subjects with SIRS, the C allele at position 4732 of SEQ ID NO: 1 (in heterozygous or homozygous form) is correlated with decreased survival and increased multiple organ dysfunction. The specification further discloses other polymorphic variations that are in linkage disequilibrium with position 4732. Of the polymorphisms that are in linkage disequilibrium with position 4732 only one, namely at position 4800 (r^2 value of 0.85) was evaluated within the same patient population as 4732 and also found to provide significant predictions of patient outcome.

Example 4 in the specification is directed to whether or not treatment with activated protein C (XIGRIS) can reduce organ dysfunction in subjects who have sepsis and who have an at risk genotype of protein C such as the C allele at position 4732. The 28 day survival rates for patients who were protein C 4732 CC/CT were compared to patients who were protein C 4732 TT with and without treatment of XIGRIS. The results indicated that XIGRIS treatment increases survival (compared to no treatment) of patients who were protein C 4732 CT/CC (See Fig 7). Further the results indicated that XIGRIS treatment had virtually no effect on survival rate over 28 days in patients who were protein C 47322 TT.

The specification does not provide enablement for the claims as broadly written. The specification teaches that in human subjects with SIRS, the C allele at position 4732 of SEQ ID NO: 1 (in heterozygous or homozygous form) is correlated with decreased survival and increased multiple organ dysfunction. Regarding the disclosed polymorphisms and combinations of polymorphisms that are in linkage disequilibrium with position 4732, only one, namely at position 4800 (r^2 value of 0.85) was evaluated within the same patient population as 4732 and also found to provide significant predictions of patient outcome. However there is no disclosed correlation between the SNP at position 4800 and increased survival when treated with XIGRIS (activated protein C).

The unpredictability of the art

While the state of the art and level of skill in the art with regard to detection of a polymorphism in a known gene sequence is high, the level of unpredictability in associating any particular polymorphism with a phenotype is even higher. The unpredictability is discussed below.

The specification teaches several genotypes and combinations of genotypes that are in linkage disequilibrium with the polymorphism at position 4732. However it is highly unpredictable if these genotypes and combinations of genotypes will also be indicative of an ability of the subject to recover from an inflammatory condition. This unpredictability is highlighted by the teachings of Langdahl (Journal of Bone and Mineral Research 2000). Langdahl teaches that linkage disequilibrium between alleles is population dependent and there can be considerable variation between the frequencies

at which alleles are inherited. For example the reference sites that while one group reported that a repeat polymorphism in the IL-1RN gene was in linkage disequilibrium with the IL-1B (+3§54) polymorphism, Langdahl et al were unable to show linkage between these polymorphisms. Additionally Wall (Nature Reviews Genetics (2003) volume 4, pages 587-597) teaches that linkage disequilibrium (LD) refers to the fact that particular alleles at nearby sites can co-occur on the same haplotype more often than is expected by chance (page 587, 1st column, 1st paragraph). Wall teaches that patterns of LD are known to be noisy and unpredictable as pairs of sites tens of kilo bases apart might be in complete LD, whereas nearby sites from the same region can be in weak LD (page 587, 2nd column, last paragraph). Wall teaches that population history, population size, and population structure lead to differences in LD (page 588, 1st column, top). Wall teaches, “Measuring LD across a region is not straightforward" (box 1, last paragraph, page 588). Wall teaches it is difficult to compare results from different LD studies directly because of the variation in study design and methods of analyzing the data (page 591, 2nd column, 1st full paragraph). Wall teaches there are clear differences in LD between African’s and non-Africans (page 593, 1st column). Thus Wall teaches that LD is not predictable. As such both Langdahl and Wall demonstrate the unpredictability in associating a genotype or a combination of genotypes in linkage disequilibrium with the polymorphism at position 4732 of SEQ ID NO: 1 with the ability of a subject to recover from an inflammatory condition.

Quantity of Experimentation

The specification teaches 2 variants in the protein C gene, namely at positions 4732 and 4800 of SEQ I DNO: 1, which are associated with altered survival and organ dysfunction in critically ill adults with SIRS. However further experimentation would be required for the claims that encompass genotypes or combinations of genotypes in linkage disequilibrium with position 4732 of SEQ ID NO: 1. One of skill in the art would have to conduct extensive experimentation to determine if each genotype or combination of genotypes is associated with the ability to recover from an inflammatory condition. Each genotype or combination of genotypes would have to be tested and analyzed to determine if it was statistically associated with a representative number of different types of inflammatory conditions. Even if the extensive experimentation was performed, there is no assurance that any other genotype or combination of genotypes would be found having the property of being associated with the ability to recover from the inflammatory condition. Such random, trial by error experimentation is considered to be undue and highly unpredictable. The specification has provided only an invitation to experiment.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the particular examples, it is the conclusion that an undue amount of experimentation would be required to make and use the claimed invention in the full scope of the claims.

Response To Arguments

4. In the response filed March 19, 2012, the Applicants traversed the enablement rejection. The Applicants state that it appears that the Examiner's only concerns with the present claims would be with an "expansion" to other polymorphisms other than 4732 of SEQ ID NO: 1 (i.e., 4054 of SEQ ID NO:2 and 2481 of SEQ ID NO: 1 and polymorphisms or combinations of polymorphisms in LD therewith). The Applicants state that they disagree that it is unpredictable that a polymorphism or combination of polymorphisms in LD with established polymorphisms are likely to lack predictive value. They assert that it is more likely than not, that such polymorphisms in LD would have predictive value. Further the Applicants disagree that the present claims would require extensive, undue experimentation. They assert that any such experimentation would be routine and predictable.

This argument has been fully considered but is not persuasive. The reply seems to be asserting that the genotypes and combinations of genotypes in linkage disequilibrium with position 4732 of SEQ ID NO: 1 could also be used to select a human subject having a risk for SIRS. However, this does not appear to be predictable based upon an analysis of the art. Just because SIRS is correlated with the SNP at position 4732 of SEQ ID NO: 1, and the SNP at position 4732 of SEQ ID NO: 1 is correlated with the genotypes and combinations of genotypes in linkage disequilibrium with position 4732 of SEQ ID NO: 1, it does not necessarily follow that the genotypes and combinations of genotypes in linkage disequilibrium with position 4732 of SEQ ID NO: 1

will also be correlated to SIRS. It appears that the reply is arguing that LD correlation is transitive, whereas the skilled artisan recognizes that correlations are not necessarily transitive. The only way to determine if genotypes and combinations of genotypes in linkage disequilibrium with position 4732 of SEQ ID NO: 1 are correlated with SIRS is to undertake a study and calculate the statistics to assess the relationship. To do this further experimentation would be required. Each of the genotypes and combinations of genotypes in linkage disequilibrium with position 4732 of SEQ ID NO: 1would have to be tested in a large population to determine if there was a statistically significant association with SIRS. Even if the extensive experimentation was performed, there is no assurance that any other genotype or combination of genotypes would be found having the property of being associated with SIRS. Such random, trial by error experimentation is considered to be undue and highly unpredictable. The applicants have not provided sufficient guidance to enable a skilled artisan to make the claimed invention in a manner reasonably correlated with the claimed method. For this reason the rejection is maintained.

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Amanda M. Shaw/
Primary Examiner
Art Unit 1634